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Evolution of Latent Hypoparathyroidism in Familial 22q11 Deletion Syndrome

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Latent hypoparathyroidism (LHP), the inability to increase midmolecular parathyroid hormone levels appropriately during a hypocalcemic challenge, was reported previously in an asymptomatic woman with tetralogy of Fallot. This woman's fourth child died with DiGeorge anomaly. Seven years later, we restudied the index patient with LHP and evaluated three generations of her family for parathyroid dysfunction, cardiac abnormalities, and del 22(q11). Deletions were found in six relatives, three with conotruncal cardiac defects and three with a structurally normal heart. We found significant transgenerational noncardiac phenotypic variability, including learning difficulties, dysmorphic facial appearance, and psychiatric illness. A spectrum of parathyroid gland dysfunction associated with the del 22(q11) was seen, ranging from hypocalcemic hypoparathyroidism to normocalcemia with abnormally low basal intact parathyroid hormone (iPTH) levels. In addition, LHP found in the index patient 7 years ago had evolved to frank hypocalcemic hypoparathyroidism. In this family, which is the largest family with 22q11 deletions studied to date, parathyroid gland dysfunction evolved over time. We suggest that the calcium parathyroid hormone axis of unrelated patients with del 22(q11) be followed closely for the development of hypocalcemic hypoparathyroidism. Am. J. Med. Genet. 69:50–55, 1997. © 1997 Wiley-Liss, Inc.

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INTRODUCTION

Seven years ago, we reported on a patient with an isolated conotruncal cardiac defect who, despite normal baseline ionized calcium and midmolecule parathyroid hormone (mm-PTH) levels, failed to increase mm-PTH secretion appropriately in response to a hypocalcemic challenge [Gidding et al., 1988]. We speculated that this combination of latent hypoparathyroidism (LHP) and conotruncal cardiac defect should be included in the clinical spectrum of the DiGeorge anomaly (DGA).

Since that time, molecular and cytogenetic studies have demonstrated that most patients with DGA have deletions within chromosomal region 22q11.2 [Carey et al., 1992; Driscoll et al., 1992]. The phenotype due to del 22(q11) is wide and includes conotruncal cardiac defects, hypocalcemic hypoparathyroidism, minor facial anomalies, and T-cell–mediated immune deficiency, as seen in DGA [Conley et al., 1974; Stevens et al., 1990; Wilson et al., 1992; Driscoll et al., 1993]. The demonstration of del 22(q11) in patients with velocardiofacial syndrome (VCFS) [Conley et al., 1974; Stevens et al., 1990; Scambler et al., 1992; Driscoll et al., 1993] and conotruncal anomaly face syndrome (CTAFS) [Shimizu et al., 1984; Burn et al., 1993] have further broadened the spectrum of clinical findings to include cleft palate, velopharyngeal insufficiency, learning disabilities, and developmental delay. Furthermore, there appears to be a broad range of phenotypic variability within families who have some characteristics of these syndromes [Holder et al., 1993; McLean et al., 1993].

Although most DGA patients have symptomatic hypocalcemic hypoparathyroidism as infants or children, those with isolated defects or "partial" syndromes can be normocalcemic with constitutively normal parathyroid hormone secretion. However, in such patients, the ability of the parathyroid glands to respond to

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hypocalcemic stress may be reduced, as seen in 50% of normocalcemic children with conotruncal cardiac defects who demonstrated LHP during cardiopulmonary bypass [Cuneo et al., 1994]. Furthermore, the functional ability of the parathyroid gland may change over time, resulting in the onset of hypocalcemic hypoparathyroidism in adolescence or young adulthood [Winter et al., 1984]. Whether LHP may precede and possibly predict the development of hypocalcemic hypoparathyroidism in these patients remains unknown.

Based on these recent molecular and metabolic advances, we restudied the index patient and evaluated three generations of her family for del 22(q11) and parathyroid gland dysfunction. We report not only multigenerational del 22(q11) with marked phenotypic variability, but a spectrum of functional parathyroid gland abnormalities, including the evolution of LHP to hypocalcemic hypoparathyroidism.

METHODS

Fluorescence In Situ Hybridization (FISH)

Metaphase chromosome spreads were prepared from peripheral blood lymphocyte cultures on each patient by standard techniques and hybridized with two cosmid DNA probes: N25 (D22S75) (Oncor, Gaithersburg, MD), a proximal marker in the DiGeorge chromosomal region (DGCR) of 22q11, and cos82, a control probe that maps to the long arm of chromosome 22 [Driscoll et al., 1993]. Hybridization was detected using avidin conjugated to fluorescein (Oncor, Gaithersburg, MD). Fifteen metaphase spreads were scored for copy number at locus D22S75.

Ca^{2+}-Intact Parathyroid Hormone (iPTH) Studies

Blood Ca^{2+} and pH were measured in duplicate with a calcium selective electrode (ICA7, Radiometer, Cleveland, OH) from 1 ml of whole blood collected in heparinized syringes, and simultaneously prepared sera were stored at −20°C until iPTH analysis. iPTH was measured in triplicate using a modification of an immunoradiometric assay (Incstar Intact PTH SP, Stillwater, MN) [Reed et al., 1990]. The normal range of iPTH in patients with a normal Ca^{2+}, is 15–55 pg/ml. In our laboratory, intra-assay variability is 5% and interassay variability is 8%.

PTH Reserve

The PTH response to hypocalcemic stress was measured in the index patient and her normocalcemic son with truncus arteriosus by methods described previously [Gidding et al., 1988]. At the time of such studies, a midmolecule radioimmune assay for PTH (mm-PTH) was used [Coe et al., 1988] rather than the terminal PTH assay that has been used since 1993. Normal values for mm-PTH are 20–80 pM.

Briefly, an infusion of disodium edetate (EDTA) was administered until the serum Ca^{2+} level fell below 1.10 mM (normal range, 1.10–1.34 mM). Serum for Ca^{2+} and mm-PTH levels were obtained every half hour for 2.5 hours. The Ca^{2+} versus mm-PTH relationship during hypocalcemic stress was evaluated by linear regression, after log transformation of the data, because mm-PTH is not normally distributed. The slope of the regression line was compared with normal controls [Gidding et al., 1988].

Echocardiography

Complete two-dimensional, Doppler, and color Doppler echocardiograms were performed on the index patient, her siblings, and her children. Her mother would not consent to the procedure. Special attention was paid to the situs of the aortic arch and the origin of the subclavian arteries.

CLINICAL REPORTS AND RESULTS

Patient 1

The index patient (II-2) is now a 34-year-old woman with repaired tetralogy of Fallot (Fig. 1). At the time of

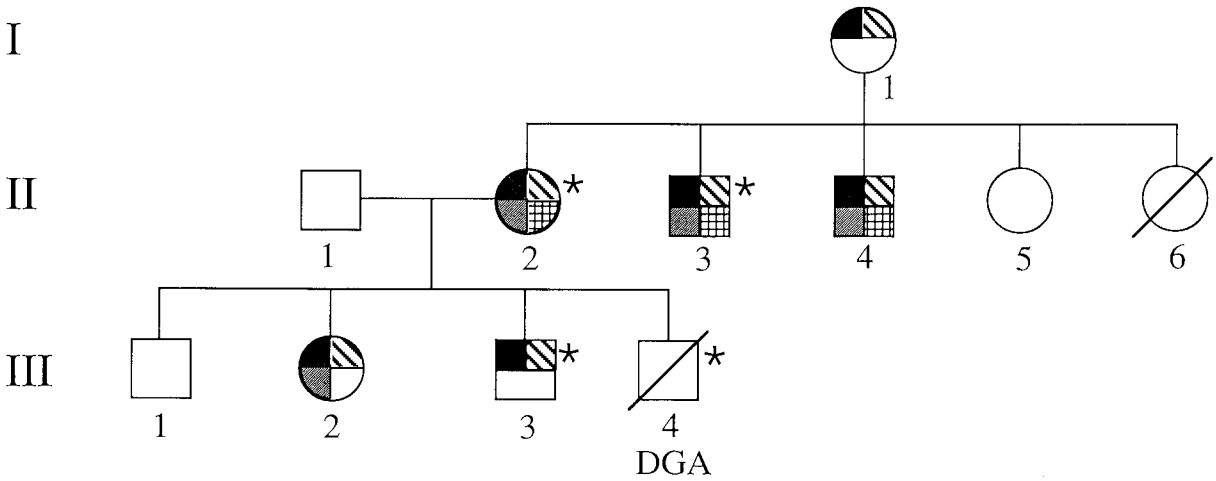

Fig. 1. Pedigree illustrating phenotypic variability of individuals with 22q11 deletion in three generations of the family reported here. ■, 22q11.2 deletion; ▧, facial dysmorphia; ■, learning disability; ▦, hypoparathyroidism; asterisk, congenital heart defect; DGA, DiGeorge anomaly.

her initial evaluation in 1987, she was normocalcemic (Ca^{2+} = 1.12 mM; normal range, 1.10–1.34 mM) with measurable mm-PTH levels. Provocative testing of her parathyroid hormone reserve documented LHP [Gidding et al., 1988]. Seven years later, she remains asymptomatic with no interval history of seizures or tetany. Nonetheless, she is frankly hypocalcemic (Ca^{2+} = 1.04 mM) with hypoparathyroidism (iPTH = 15 pg/ml); her magnesium and vitamin D levels are normal. She has many manifestations of the del 22(q11) syndrome, including prominent circular ears, a small mouth, and ocular hypertelorism [Strong et al., 1968; Kinouchi et al., 1976]. In addition, she has hypernasal speech suggestive of velopharyngeal insufficiency. Until recently she lived in a group home, but is currently hospitalized in a psychiatric institution, complaining of auditory hallucinations. FISH studies demonstrated a deletion of locus D22S75 (N25) in the "DiGeorge chromosomal region" (DGCR).

The family history is remarkable. Her paternal grandfather died in 1955 after surgical repair of coarctation of the aorta. One brother (II-3) also has tetralogy of Fallot. One son (III-4) died with complete DGA (type B interrupted aortic arch with thymic and parathyroid gland aplasia); a second son (III-3) has truncus arteriosus.

Patients 2 (II-3) and 3 (II-4)

The index patient has two brothers with del 22(q11). Patient 2, age 34, has tetralogy of Fallot. Following two syncopal episodes with seizures at age 33, electrophysiologic testing showed monomorphic ventricular tachycardia with a cycle length of 200 msec. His electroencephalogram was abnormal as well, but Ca^{2+} levels were not measured. Since that time, he has been treated with sotalol and phenytoin, with no recurrence of syncope or seizures.

Four months before cardiac surgery in 1992, his total calcium was 8.1 mg/dL (normal range, 8.5–10.2 mg/dL). Currently, he is hypocalcemic (Ca^{2+} = 0.89 mM) with an inappropriately low iPTH (29 pg/ml), but he has normal serum levels of magnesium, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D. He has no muscle cramps, tetany, Trousseau, or Chvostek sign. His cerebral computed tomography shows no intracerebral or basal ganglion calcifications.

In addition to facial characteristics shared by his sister, Patient 2 has a very prominent nasal tip, a "fish-like" mouth, and a short philtrum (Fig. 2, left). Patient 2 developed paranoid schizophrenia in his late 20s and has been treated with molidine HCl and clozapine for 3 years. He lives in a group home and works in a sheltered environment.

Patient 3 (II-4), age 31, the second brother of the index patient, has a structurally normal heart with a left aortic arch and normal origin of both subclavian arteries. Like his sister and brother, he has asymptomatic hypocalcemic hypoparathyroidism (Ca^{2+} = 0.92 mM, iPTH = 8 pg/ml) with normal magnesium and vitamin D levels; he also has a del 22(q11). He has hypertelorism, a short philtrum, and a small mouth. Although he has been diagnosed with chronic schizophrenia, he is taking no medications. He lives independently and is employed.

Patient 4 (I-1)

The mother (age 60) of the index patient has no discernible congenital heart disease, although a right aortic arch or anomalous origin of the subclavian arteries could not be excluded. Although she too manifests a 22q11 deletion by FISH, serum Ca^{2+} and iPTH levels are normal (1.13 mM and 42pg/L, respectively). She is mildly abnormal in appearance with hypernasal speech. Although she lives a reclusive life and is eccentric, she carries no formal psychiatric diagnosis. She completed business college and has been employed. There is no history of congenital heart disease, mental illness, seizures, or palatal abnormalities in her parents or grandparents.

Patient 5 (III-3)

The second affected child of the index patient was diagnosed prenatally with truncus arteriosus. After birth, Ca^{2+} and iPTH levels were normal. At age 4 years, his PTH reserve was evaluated by EDTA-induced hypocalcemia. Similar to his mother, he had normal baseline Ca^{2+} and mm-PTH levels (1.27 mM, 16 pM) but demonstrated LHP (Table I). Now 10 years old, he remains asymptomatic. He is in an age-appropriate grade and has no evidence of learning disabilities. He has some midfacial hypoplasia and a small mouth. His Ca^{2+} is normal (1.3 mM), but he has no measurable iPTH (< 2 pg/mL). He too has a del 22(q11) detected by FISH.

Patient 6 (III-2)

The facial appearance of the index patient's 14-year-old daughter resembles that of her maternal uncle; she has small almond-shaped palpebral fissures and a prominent nasal tip (Fig. 2, right). She has a 22q11 deletion, a structurally normal heart with a left aortic arch, and normal origin of the subclavian arteries. Like her brother, she has a normal basal Ca^{2+}, but an iPTH level of only 8 pg/mL. She has not been evaluated for LHP. She manifests no behavior disturbances, but does have a learning disability.

Other Relatives

The index patient's youngest sister (II-6) died at 3 months in 1971 of sudden infant death syndrome. The only abnormality noted on autopsy was a single kidney. The other sister and their father have normal echocardiographic findings, a normal baseline Ca^{2+}, and measurably normal iPTH levels. They do not have a 22q11 deletion.

DISCUSSION

We have described three generations of individuals with del 22(q11) whose presentation varied from minor facial anomalies and an eccentric personality to interrupted aortic arch with thymic and parathyroid gland aplasia. This family demonstrates the transition from normocalcemia to frank hypocalcemia, and from LHP to hypocalcemic hypoparathyroidism. These findings confirm that there can be substantial transgenera-

Fig. 2. Facial photographs of two affected relatives demonstrating minor facial anomalies of the del 22 (q11) syndrome. See Figure 1 for generational identification of these patients. **A**: Patient 2 (II-3), brother of the index patient. Note the bulbous nasal tip, "fish-like mouth," and short philtrum. **B**: Patient 6 (III-2), daughter of index patient, has small almond-shaped palpebral fissures and prominent nasal tip.

tional phenotypic variability in the del 22(q11) syndrome. Furthermore, because LHP has evolved into hypocalcemic hypoparathyroidism, other relatives with the deletion are at risk for the development of hypocalcemia. These findings raise the possibility that unrelated patients with manifestations of the del 22(q11) syndrome may be at risk for the development of hypocalcemic hypoparathyroidism.

The syndromes that share del 22(q11) as a cause include one or more of the following anomalies: congenital cardiac defects (usually of the outflow tracts or ventricular septum), T-cell–mediated immune deficiency, parathyroid gland dysfunction, palatal defects, cognitive impairment, and minor facial anomalies. Within each there is a wide spectrum of clinical expression. For example, psychosocial developmental changes may range from mild learning disabilities to profound antisocial personalities with severe psychiatric conditions, and palatal anomalies range from hypernasal speech to an overt cleft palate. Cardiac involvement ranges from the incidental finding of a right aortic arch to severe low cardiac output from type B interrupted aortic arch. Even within one family, the variability may be as great as between unrelated individuals, as seen in the largest family described here and in smaller families [Wilson et al., 1991; Holder et al., 1993; McLean et al., 1993].

At the present time, the size and extent of the deletion does not account for the phenotypic variability [Driscoll et al., 1995]. However, additional studies will be necessary to define more precisely the deletion boundaries and to determine if the size of the deletion differs among members of this family.

The spectrum of parathyroid gland dysfunction in the del 22(q11) syndrome is less well characterized than its other manifestations. Absent parathyroid tissue with hypocalcemia is well recognized in patients with DGA. Hypocalcemic hypoparathyroidism has been described in adolescents with del 22(q11) and VCFS [Scire et al., 1994]. Infants, who later are shown to have del 22(q11), have presented with hypocalcemic hypoparathyroidism that spontaneously improves in childhood and then recurs in adolescence or young adulthood [Paul et al., 1994]. Normocalcemia has been shown to evolve to hypocalcemic hypoparathyroidism in a patient presenting with seizures [Winter et al., 1984].

However, more subtle alterations in parathyroid gland secretory function, as seen in this family, may not be recognized. Even the finding of hypocalcemic hypoparathyroidism in the index patient and her brothers

TABLE I. Midmolecule PTH Levels in Response to EDTA-Induced Hypocalcemia in a Patient (III-3) From the Reported Family With 22q11 Deletion*

Time (hours)	Ca^{2+} (mM)	mm-PTH (pM)
0	1.27	16
0.5	1.17	64
1.0	1.14	69
1.5	1.13	63
2.0	1.08	64
2.5	1.09	49
4.0	1.24	18

*EDTA, disodium edetate; Ca^{2+}, blood ionized calcium (normal values, 1.10–1.34 mM); mm-PTH, midmolecule parathyroid hormone (normal values for normal Ca^{2+} levels, 20–80 pM). EDTA was infused after the values obtained at time 0 hours through 2.5 hours to lower Ca^{2+} sequentially. At each time point during EDTA infusion, the level of mm-PTH achieved was less than that achieved in normal adults undergoing the identical protocol.

was unexpected, because of the insidious onset of parathyroid gland dysfunction in the fourth decade of life, its lack of overt symptoms, and the phenotypic variability among the relatives. Based on the results herein, we believe that there are three different manifestations of parathyroid dysfunction in the del 22(q11) syndrome. LHP, the inability to augment PTH secretion appropriate to a hypocalcemic stimulus, was demonstrated 7 years ago in the index patient and 5 years ago in her son. Another manifestation of parathyroid dysfunction occurs in the setting of normocalcemia and produces an abnormally low basal iPTH level, as seen in the index patient's daughter and son. Finally, the development of frank hypocalcemic hypoparathyroidism may occur. This was demonstrated in the index patient and her two brothers. Additionally, at least in the index patient, we documented its evolution following LHP.

The mechanism of diminished iPTH secretion in del 22(q11) is currently unknown. Studies in a chick embryo model of DGA suggest that induced abnormalities of neural crest cells may contribute to disturbances in parathyroid gland function [Kirby et al., 1983; Bockman et al., 1984]. The finding of decreased numbers of thyrocalcitonin-containing cells derived from cranial neural crest in patients with DGA further supports the role of neural crest cells in the development of this disturbance in the del 22(q11) syndrome [Palacios et al., 1993]. Therefore, it has been hypothesized that haploinsufficiency of the gene(s) in the DGCR results in abnormal neural crest cell development or migration. Because autopsy studies have shown hypoplasia of the parathyroid glands in some patients with DGA, this haploinsufficient state may result in hypoplasia of the secretory portion of the parathyroid gland. The functional manifestation becomes apparent only with increasing age or during periods of evoked hypocalcemic stress.

Thus, del 22(q11), which produces a variety of systemic disturbances in children, must now be recognized as a potential cause of hypocalcemia in the adult. The calcium parathyroid axis should be evaluated in patients with clinical features or a family history suggestive of the del 22(q11) syndrome. Conversely, careful scrutiny for the phenotypic characteristics of the del 22(q11) syndrome should be undertaken in the evaluation of hypocalcemia. Finally, long-term follow-up should be given to patients with normocalcemia in the del 22(q11) syndrome because of its natural evolution to hypocalcemic hypoparathyroidism.

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